

Clinical Monograph: Hormone Replacement Therapy

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ABSTRACT

BACKGROUND: For decades, hormone replacement therapy (HRT), which includes both estrogen and progestin, has been administered to postmenopausal women to mainly treat the symptoms of menopause and help prevent osteoporosis, with the added benefit of preventing coronary heart disease (CHD). Recently released study results have left clinicians wondering if HRT should be used at all, and, if so, with whom and under what circumstances.

OBJECTIVE: To provide readers with an example of the real-world operation of a pharmacy and therapeutics (P&T) committee in its use of a concise clinical monograph to guide its formulary decisions.

METHODS: The most relevant information for this committee, interested in evidence, was an analysis of the most current pivotal trials and observational studies that help define the place in therapy of HRT and provide information on product efficacy and safety. These included the Heart and Estrogen/progestin Replacement Study (HERS) and its extension trial, HERS II, in postmenopausal women with CHD and an average age of 67 years. The Women's Health Initiative (WHI) study, where the mean age of postmenopausal women was 63 years was also reviewed. The U.S. Food and Drug Administration (FDA) statements through January 8, 2003, on the appropriate use of these agents were also included in this clinical monograph for P&T committee review.

RESULTS: HERS and HERS II provided evidence that HRT does not provide secondary prevention in women with CHD. Data from the WHI study concluded that HRT promotes CHD and breast cancer in this age group. The Women's Health, Osteoporosis, Progestin, Estrogen study concluded that lower doses of conjugated estrogens (0.3 mg) are just as effective in treating postmenopausal symptoms as higher doses (0.625 mg) and result in fewer side effects.

CONCLUSION: The risk of breast cancer outweighs the benefits of osteoporosis prevention from HRT. According to labeling changes recommended by the FDA, HRT (or estrogen replacement therapy) should be limited to the shortest possible duration. Alternatives to HRT should be considered for the prevention of postmenopausal osteoporosis.

KEYWORDS: Hormone replacement therapy, Estrogen replacement therapy, HERS trial, Women's Health Initiative trial, Osteoporosis, Menopause, Coronary heart disease

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This study discusses an excerpt from a clinical monograph on hormone replacement therapy (HRT) that was used by the pharmacy and therapeutics (P&T) committee of an integrated health network (IHN); the committee has a total membership of 28 physicians and pharmacists who represent both hospitals and medical groups. Information in this monograph was used as the basis for decision making by the P&T committee in February 2003 about HRT products.

Because of the recent release and availability of new data from clinical trials and observational studies, the committee was asked to decide whether various HRT products should be on the IHN formulary, and, if so, which ones. This HRT clinical monograph had been used by one medical group as a resource for developing clinical use guidelines. Two weeks prior to the P&T committee meeting, a binder that included this monograph was mailed to all P&T committee members. The clinical information was also presented at the P&T meeting in a brief (5 to 10 minute) verbal summary. After the committee meeting, more information was released from the Women's Health Initiative (WHI) study that HRT does not guard against Alzheimer's disease, and, in fact, may increase the risk of developing it.^{1,2}

Clinical safety and efficacy were considered first by the P&T committee. Health plan formulary coverage, placement (copayment tier), and relative cost were also considerations in the decision-making process. The cost of HRT is mostly an outpatient (health plan) concern since patients are in the hospital for only a few days but may take HRT for years as an outpatient.

The IHN provides hospital and medical services to the commercial membership of 5 health plans, which retain the financial risk for outpatient drugs except injectables. Therefore, the IHN P&T Committee is concerned primarily with the practical effects on continuity of care and coordination between inpatient and outpatient care. Placement of the specific products in the generic tier or in the preferred-brand tier is considered for the 5 major health plans that insure the patients in this IHN. If a drug is not covered or not preferred, the patients cannot readily receive the drug at pharmacies due to processes put in place by the 5 health plans. For example, physicians have to request permission to use the drug, usually in the form of a prior authorization, if the drug is not covered or, in some cases, if the drug is simply not preferred. The extra time consumed in paperwork and phone calls is sufficient to deter most prescribers from using nonformulary drugs.

For the IHN P&T Committee, an attempt was made to obtain drug product dossiers in the AMCP format³ from the manufacturers of the key products in the current WHI clinical trial, the combination estrogen and progestin products. These

products were selected from all the products in this class because the medical literature is largely focused on conjugated equine estrogens (CEEs) and medroxyprogesterone acetate (MPA), the hormones used in the WHI and HERS studies.⁴ Given the desire by the audience for concise presentation of selected relevant data, other product dossiers were not obtained. The dossiers of the selected products were not available at the time this monograph was written. MEDLINE searches provided primary research articles. Some information, including analyses of the WHI data, was obtained through continuing education program presentations for pharmacists. General information was taken from review articles, textbooks, and product prescribing information.

■ Monograph Format

The clinical monograph followed the drug monograph format used by the University Health-System Consortium (UHC),⁵ and includes sections for Indications, Pharmacology, Pharmacokinetics, Clinical Efficacy, Adverse Events, Drug Interactions, Dosing and Administration, Availability, and Conclusions. UHC sells its monographs to many hospitals and pharmacy benefit managers (PBMs) that have formularies and use the P&T process to add and delete drugs from their drug formularies. For the P&T committee of this IHN, the most important section is Clinical Efficacy, followed by the Adverse Events section, then Pharmacology and Pharmacokinetics, Drug Interactions, and, lastly, Indications, Dosing and Administration, and Availability.

The Indications section is important for organizations such as PBMs and health maintenance organizations that select formulary drugs based on their U.S. Food and Drug Administration (FDA)-approved indications. Pharmacokinetic and pharmacologic properties can be unique among products in the same therapeutic class and can be deciding factors in drug choices. For example, if a drug has a unique mechanism of action, it might be included because it offers an alternate approach to therapy. A drug that bypasses first-pass metabolism, through dermal or vaginal administration, for example, can be given in a lower dose and perhaps result in fewer adverse effects. If a drug in the class has a serious safety threat—for example, it causes hepatic failure in some patients—it would be unlikely that the drug would be added to the formulary. If a drug in the class has more drug interactions than the others, it is not likely to be added to the formulary, due to possible deleterious effects from unnoticed drug interactions when prescribed and dispensed. Dosing and Administration and Availability address the concerns of patient compliance and convenience, among others. For example, patients are more likely to be compliant with a drug taken once daily than a drug that has to be taken 3 times daily.

Indications

The indications approved by the FDA for use of the estrogens

TABLE LEGENDS

<i>B</i> = blinded	<i>MI</i> = myocardial infarction
<i>CABG</i> = coronary artery bypass graft	<i>MPA</i> = medroxyprogesterone acetate
<i>CEE</i> = conjugated equine estrogen	<i>NS</i> = not significant
<i>CHD</i> = coronary heart disease	<i>OL</i> = open label
<i>CI</i> = confidence interval	<i>PC</i> = placebo controlled
<i>CVD</i> = cardiovascular disease	<i>PE</i> = pulmonary embolism
<i>DVT</i> = deep venous thrombosis	<i>PTCA</i> = percutaneous transluminal coronary angioplasty
<i>ERT</i> = estrogen replacement therapy	<i>R</i> = randomized
<i>HDL</i> = high-density lipoprotein	<i>RH</i> = relative hazard
<i>HRT</i> = hormone replacement therapy	<i>RR</i> = relative risk
<i>IHN</i> = integrated health network	<i>SD</i> = standard deviation
<i>ITT</i> = intention-to-treat	<i>VTE</i> = venous thromboembolism
<i>LDL</i> = low-density lipoprotein	
<i>MC</i> = multicenter	

were summarized in table form for this monograph (Table 1). It was noted that progestins, which are not available except as combination products with estrogen, do not have FDA approval as adjunctive therapy or sole therapy to treat menopausal vasomotor symptoms or to prevent or treat osteoporosis.⁶

Pharmacology

Estrogens are responsible for the development and maintenance of the female reproductive system and secondary sexual characteristics. Estradiol is the principal human estrogen and is substantially more potent than its metabolites, estrone and estrinol at the receptor. The primary source of estrogen in normally cycling adult women is the ovarian follicle, which secretes 70 mcg to 500 mcg of estradiol daily, depending on the phase of the menstrual cycle.

The underlying cause of the onset of menopause is an age-related loss of ovarian function that results in a decline in estrogen secretion by the ovarian follicular unit. Most follicles are lost due to follicular atresia, a normal physiologic process of degeneration of the oocyte and its surrounding stroma.⁷ Although some follicles remain in postmenopausal women, they are less sensitive to gonadotropin stimulation, implying that the more hormonally sensitive or functionally normal follicles are depleted earlier in life.⁷

After menopause, most endogenous estrogen is produced by conversion of androstenedione, secreted by the adrenal cortex, to estrone by peripheral tissues. In postmenopausal women, estrone and the sulfate-conjugated form, estrone sulfate, are the most abundant circulating estrogens. Postmenopausal decline in ovarian estradiol production causes diminished negative-feedback effects on the anterior pituitary glands, which results in a compensatory increase in secretion of the gonadotropins, follicle-stimulating hormone, and luteinizing hormone (LH).⁸

Estrogens act through binding to nuclear receptors in estrogen-responsive tissues. Two estrogen receptors (ER) have been identified—alpha and beta. ER alpha is present on endothelial

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TABLE 1 FDA-Approved Indications for Estrogens⁶

	Vasomotor Symptoms of Menopause	Osteoporosis Prevention	Abnormal Uterine Bleeding	Atrophic Vaginitis	Kraurosis Vulvae	Female Hypogonadism	Female Castration	Primary Ovarian Failure	Metastatic Breast Cancer (Palliative)	Prostate Cancer (Palliative in Advanced Disease)
Estradiol oral										
Estradiol oral	x	x		x	x	x	x	x	x	x
Ethinyl estradiol	x					x			x	x
Estradiol transdermal										
Estradiol patch	x	x	x	x	x	x	x	x		
Estradiol injectable										
Estradiol valerate	x			x	x	x	x	x		x
Estradiol hemihydrate				x						
Estradiol cypionate in oil	x					x				
Other estrogens										
CEE (conjugated equine estrogens)	x	x	x*	x		x	x	x	x	x
Synthetic conjugated estrogens A	x									
Esterified estrogens	x			x	x	x	x	x	x	x
Estrone	x			x	x	x	x	x	x	x
Estropipate	x	x		x	x	x	x	x		
Vaginal estrogens										
Miscellaneous vaginal creams†				x	x					
Combination estrogens and progestins										
Estrogens and progestins, combined in women with intact uterus	x	x‡		x§	x	x	x	x		

* Injectable formulation only.

† Contains either estradiol, conjugated estrogens, or estropipate.

‡ Combipatch excluded.

§ Femhrt excluded.

|| Combipatch only.

and smooth muscle cells. ER beta is present in human arteries, veins, and myocardial cells.⁹ Women with ER-alpha receptor polymorphism, called IVSI-401 c/c, have high-density lipoprotein (HDL) increases 2 times the extent seen in other women.¹⁰

Symptom complexes related to estrogen deprivation include genitourinary atrophy and vasomotor instability. Vasomotor symptoms or hot flashes most often prompt postmenopausal women to seek medical care. The cause of these symptoms is estrogen deficiency, possibly leading to aberrant surges of LH or gonadotropin-releasing hormone,¹¹ which affect the hypothalamic neurons that control central thermoregulation centers. They are most common within 12 to 24 months after the last menstrual period, gradually subsiding thereafter. The hot flush is an acute, episodic event that initially occurs several times a day, often during sleep. Peripheral blood flow increases, causing increased skin temperature. Perspiration occurs as a homeostatic response designed to dissipate heat. An increase in heart rate probably reflects a sympathetic response to change in skin temperature.¹² Estrogen has traditionally been the drug of choice for relieving hot flashes, but MPA in relatively high doses, some

ergot alkaloids, clonidine,¹² venlafaxine,¹³ and paroxetine¹⁴ are also effective.

Treatment with intravaginal or systemic estrogen reverses the thinning of the vaginal mucosa through epithelial proliferation and decreases vaginal pH to its more normal acidic state. The higher pH that occurs during menopause creates a favorable environment for bacterial colonization by various pathogens. Estrogen therapy often relieves symptoms of vaginitis and frictional dyspareunia.^{7,15}

Progesterone is a secretory product of the corpus luteum. Progestins act on the endometrium to change proliferative endometrial tissue into secretory tissue. Progestins alone are as effective as estrogens for relief of vasomotor symptoms. They are useful in the treatment and prevention of osteoporosis and appear to stimulate bone formation via androgenic and anabolic effects.¹⁶ The addition of progestin for 12 days each month with estrogen replacement therapy serves 3 major purposes: to decrease the risk for estrogen-induced irregular bleeding, endometrial hyperplasia, and carcinoma; to protect against breast carcinoma; and to enhance estrogen prophylaxis of osteoporosis.¹⁷

TABLE 2 Heart and Estrogen/Progestin Replacement Study (HERS) Trials

METHODS	RESULTS			
HERS (JAMA. 1998.)¹⁸				
Objective: To determine if estrogen plus progestin therapy alters the risk for CHD events in postmenopausal women with established coronary disease.	Overall, there were no significant differences between groups in the primary outcome or in any of the secondary cardiovascular outcomes.			
Methods: R, B, MC, PC secondary prevention trial in U.S. n = 2,763 women with coronary disease, younger than 80 years, and postmenopausal with an intact uterus. Mean age was 66.7 years.		HRT	Placebo	RH (95% CI)
Interventions: n = 1,380 conjugated equine estrogen (CEE) 0.625 mg plus 2.5 mg of medroxyprogesterone acetate (MPA) in 1 tablet daily	MI or CHD death	n=172	n=176	0.99 (0.80-1.22)
n = 1,385 placebo	VTE	n=34	n=12	2.89 (1.50-5.58)
Follow-up averaged 4.1 years.	Gall bladder disease	n=84	n=62	1.38 (1.00-1.92)
Outcomes: The primary outcome was the occurrence of non-fatal MI or CHD death. Secondary cardiovascular outcome included coronary revascularization, unstable angina, congestive heart failure, resuscitated cardiac arrest, stroke or transient ischemic attack, and peripheral arterial disease. All-cause mortality was also evaluated.	Lipid Profiles	HRT Compared With Placebo		P value
	LDL	HRT 11% lower		P<0.001
	HDL	HRT 10% higher		P<0.001
	There was a statistically significant time trend, with more CHD events in the hormone group than in the placebo group in year 1 and fewer in years 4 and 5. There were no significant differences in other endpoints for which power was limited, including fracture, cancer, and total mortality.			
HERS II Cardiovascular Outcomes (JAMA. 2002.)¹⁹				
Objective: To determine if the risk reduction of CHD noted in years 3 to 5 in the HERS trial persisted and resulted in an overall reduced risk of CHD events with additional years of follow-up.	There were no significant decreases in rates of primary CHD events or secondary cardiovascular events among women assigned to the hormone group compared with the placebo group in HERS, HERS II, or overall.			
Methods: R, B, PC trial of 4.1 years duration (HERS) and subsequent unblinded follow-up for 2.7 years (HERS II) conducted at 20 outpatient U.S. centers.		CHD Events RH (95% CI)		
n = 2,321 of the original 2,763 women in HERS who were part of unblinded follow-up for 2.7 years. In other words, this is data from the HERS group of women, extended for an additional 2.7 years.	HERS unadjusted	0.99 (0.81-1.22)		
Interventions: Open-label hormone therapy was prescribed at personal physician's discretion during HERS II. The proportions with at least 80% adherence to hormones declined from 81% (year 1) to 45% (year 6) in the hormone group and increased from 0% (year 1) to 8% (year 6) in the placebo group.	HERS II unadjusted	1.00 (0.77-1.29)		
Outcomes: The primary outcome was nonfatal myocardial infarction and CHD death. Secondary cardiovascular outcomes were coronary revascularization, hospitalization from unstable angina or congestive heart failure, nonfatal ventricular arrhythmia, sudden death, stroke or transient ischemic attack, and peripheral arterial disease.	HERS + HERS II combined, unadjusted	0.99 (0.84-1.17)		
	HERS + HERS II combined, adjusted*	0.97 (0.82-1.14)		
	Women adherent to randomized treatment	0.96 (0.77-1.19)		
	*Data adjusted for potential confounders and differential use of statins between treatment groups.			
	The authors concluded that 6.8 years of hormone therapy did not reduce the risk of cardiovascular events in women with CHD.			
HERS II Noncardiovascular Outcomes (JAMA. 2002.)²⁰				
Objective: To evaluate the long-term effect of postmenopausal hormone therapy on common noncardiovascular disease outcomes.	Comparing ITT women given HRT with placebo in combined data from HERS and HERS II. RH (95% CI) data presented.			
Design: R, B, PC trial of 4.1 years duration (HERS) and subsequent OL observational follow-up for 2.7 years (HERS II) between 1993 and 2000 at 20 U.S. outpatient settings.		HERS + HERS II	P Value	
Intervention: See HERS II above.	DVT/PE	2.08 (1.28-3.4)	0.003	
Outcomes: Thromboembolic events, biliary tract surgery, cancer, fracture, and total mortality.	Biliary tract surgery	1.48 (1.12-1.95)	0.005	
	Any fracture	1.04 (0.87-1.25)	0.66	
	Breast cancer	1.27 (0.84-1.94)	0.26	
	CVD death	1.11 (0.89-1.39)	0.36	
	Any death	1.10 (0.92-1.31)	0.29	
	Adjusted and as-treated analyses did not alter the investigators' conclusions.			

Pharmacokinetics

The products in this class differ by administration route, which affects dose and adverse effects, and by the potency of the type of estrogen in the product. In an effort to be concise, only these pharmacokinetic issues are addressed.

Oral administration may utilize estradiol, conjugated estro-

gens, esters of estrone, or ethinyl estradiol. Estradiol is not used frequently by mouth because of extensive first-pass hepatic metabolism. A micronized version of estradiol yields a large surface area for rapid absorption, yet high doses must be used because absolute bioavailability remains low.

The ethinyl substitution in the C-17 position inhibits first-

TABLE 3 Women's Health Initiative (WHI) Study²¹

METHODS	RESULTS
<p>Objective: An NIH/NHLBI*-sponsored study to determine the risk vs. benefit of ERT vs. continuous HRT (conjugated estrogens with medroxyprogesterone) in postmenopausal women</p> <p>Methods: n = 27,000 women aged 50-79 years, between 1993 and 1998; scheduled to conclude in 2005. Mean age~63 years. Most women were ≥10 years postmenopausal. Only one third were between the ages of 50 and 60 years. N~16,000 stopped therapy and included in current publications.</p> <p>Interventions: 3 arms to study: 1. placebo 2. Continuous HRT-CEE 0.625 mg/MPA 2.5 mg once daily 3. ERT arm for patients without a uterus n ~10,000 in ERT arm, which is still ongoing</p> <p>Outcomes: Global Index (not an index that has been studied and proven valid) 1. CHD events (nonfatal MI, CHD death) 2. Breast cancer 3. Stroke 4. Pulmonary embolism 5. Endometrial cancer 6. Colorectal cancer 7. Hip fracture 8. Deaths due to other causes</p>	<p>The benefits of therapy were decreased risk of colorectal cancer and fractures. The study showed a statistically significant increase in risk of CHD, strokes, VTE/PE. After 4 years of therapy, an increase of invasive breast cancer was noted.</p>

Note: These were postmenopausal women, and symptoms common during menopause such as vaginal atrophy were not included.

**National Institutes of Health /National Heart, Lung, and Blood Institute.*

pass metabolism of ethinyl estradiol. CEEs are primarily the sulfate esters of estrone, equilin, and other naturally occurring compounds. Esterified esters are mixtures of conjugated estrogens prepared from plant-derived sources. The esters are hydrolyzed by enzymes in the lower gut, removing the charged sulfate group and allowing the absorption of estrogen. Estropipate is estrone solubilized by sulfate and stabilized with piperazine.²²

During first-pass metabolism of orally administered estrogen, about 60% to 90% of the dose of estrogen is metabolized to estrone or inactive metabolites. High doses of exogenous estrogens must be administered to compensate for this effect.²³

Estrogen in vaginal creams is readily absorbed through the vaginal epithelium. Estradiol is metabolized very little as it is absorbed from the vagina, and this route of administration results primarily in increased estradiol serum concentrations. But these concentrations return to baseline in approximately 6 hours. Because of the short duration of increased serum concentrations and because vaginal creams are messy, they are not widely used.²⁴

The transdermal patch, containing estradiol, offers therapy with no first-pass metabolism of estradiol, convenient administration, and precise dosing.²⁴ Administration of estradiol via transdermal patches provides slow, sustained release of the hormone and more constant blood levels. Oral administration exposes the liver to high concentrations of estrogens via the portal circulation and causes a more rapid conversion of estradiol or conjugated estrone to estrone. Both of these effects are lessened with transdermal estradiol.²² Transdermal administration results in estradiol levels equivalent to those in the early-to-mid-follicular phase and an estrone-to-estradiol ratio of

approximately 1 to 1, which closely resembles the premenopausal state.²⁵ Oral administration can achieve similar estradiol levels, but only at the expense of a higher estrone-to-estradiol ratio.²⁶

Progesterone is poorly absorbed when administered orally, and thus synthetic forms of 17-hydroxyprogesterone and 19-nortestosterone are used clinically. MPA is the progestin used in treating menopausal symptoms because it is relatively well absorbed orally and has a more acceptable side-effect profile than 17-hydroxyprogesterone or 19-nortestosterone.²⁷

Clinical Efficacy

The Heart and Estrogen/progestin Replacement Study (HERS, HERS II) (Tables 2 and 8) and WHI (Tables 3 to 7) studies are the pivotal studies with regard to defining the risks of HRT (Table 2). The findings of HERS and HERS II about the lack of benefit of HRT in cardiovascular high-risk women are supported by findings of 2 randomized trials that assessed the effect of HRT on progression of atherosclerosis.^{28,29}

The Estrogen Replacement Atherosclerosis trial³⁰ randomized 309 postmenopausal women with angiographically verified coronary disease to receive placebo, estrogen replacement therapy (ERT) as 0.625 mg/d of conjugated equine estrogen, or HRT as daily estrogen plus progestin, as in HERS. After 3.2 years of follow-up, the mean minimal coronary artery diameter on repeat coronary angiograms was not significantly different among women assigned to placebo, ERT, and HRT. The findings were unchanged in an analysis limited to patients who complied with treatment.

In the Postmenopausal Hormone Replacement Against Atherosclerosis trial, 321 postmenopausal women with

TABLE 4 WHI Baseline Characteristics³³

Characteristic	HRT (n = 8,506)	Placebo (n = 8,102)
Age at screening, years in mean (SD)	63.2 (7.1)	63.3 (7.1)
Prior hormone use (%)	26.1	25.6
Body mass index, kg/m ² in mean (SD)	28.5 (5.8)	28.5 (5.9)
Never smokers (%)	49.6	50.0
Diabetes (%)	4.4	4.4
Hypertension (%)	35.7	36.4
Statin use at baseline (%)	6.9	6.8
Family history breast cancer (%)	16.0	15.3
History of MI (%)	1.6	1.9
History of CABG/PTCA	1.1	1.5, P = .04

Note: These patients had some risks for cardiovascular disease: 36% had hypertension, 4.4% had diabetes, 50% had a history of smoking. At baseline, this could be interpreted as asymptomatic early heart disease in many of these patients.

TABLE 5 WHI Results: Summary of Main Outcomes³³

Outcome	Relative Risk vs. Placebo* Nominal 95% CI†	Increased Absolute Risk per 10,000 Women/Year	Increased Absolute Benefit per 10,000 Women/Year
CHD	1.29 (1.02-1.63)	+7	
Invasive breast cancer	1.26 (1.00-0.59) NS	+8	
Stroke	1.41 (1.07-1.85)	+8	
VTE	2.11 (1.58-2.82)	+18	
Colorectal cancer	0.63 (0.43-0.92)		-6
Hip fracture	0.66 (0.45-0.98)		-5
Global index	1.15 (1.03-1.28)		
Death due to other causes	0.92 (0.74-1.14) NS		
Total death	0.98 (0.82-1.18) NS		

*The relative risk or hazard ratio is not generally important unless >2. If it is 1, there is no relative risk; if <1, it is protective.

†If the 95% CI hits 1, it is not significant. Nominal 95% CI is variability based on a single outcome measured at one point in time. In contrast, the adjusted 95% CI corrects variability for multiple analyses over time.

nonfatal stroke in women assigned to ERT was 1.0 (95% CI, 0.7-1.4). In the HERS trial, HRT, according to 95% CIs, was not significantly associated with the risk of nonfatal stroke, fatal stroke, or transient ischemic attack.

In the WHI study, the HRT arm, but not the ERT arm, was stopped early, after 5.2 years of follow-up. The safety monitoring board determined that the risks of continuous HRT outweighed the benefits. The increased risks were cardiovascular disease (CVD), strokes, thromboembolic disorders, and invasive breast cancer. The increased risk did not include mortality.

In the fifth year, in the WHI study, there were 2,000 fewer patients in each group, making the placebo event rate of 9 in year 5 lower than expected for this age group, increasing the hazard ratio. The data >5 years was not powered to detect any significant differences. The hazard ratio that is significant, however, is the one in the first year, which shows that the risk does go up (see Table 7).

One hypothesis for why the risk is greater in the first year is that prevention of coronary heart disease (CHD) requires therapy soon after menopause. These were not all healthy patients at baseline: 36% had hypertension, 4.4% had diabetes, 50% had a history of smoking (see Table 4). They could be regarded as asymptomatic women with atherosclerosis. These were also older women, who are less likely to have reversible atherosclerosis. The authors concluded that HRT leads to an increased risk of myocardial infarction (MI), deep venous thrombosis (DVT), and venous thromboembolism (VTE). Here MIs were silent; MIs were identified by EKG changes.

If a Kaplan-Meier estimate is drawn from the WHI data with the cumulative hazard for CHD on the y axis and time in years on the x axis, then plotting the HRT group versus the placebo shows that the largest divergence between the 2 lines occurs within the first 2 years, then the 2 lines run parallel to each other thereafter. The same higher risk for CHD in the first 2 years was also seen in the HERS data.

As shown in Table 8 for the HERS trial, the number of placebo events in the first year (38) is less than expected, increasing the hazard ratio. The first-year hazard ratio could have been due to chance alone because when the study was extended out 2.8 more years, the outcome of a hazard ratio <1 continued.

Finally, there is a hypothesis that there is some subset of women who have an increased risk of CHD due to some genetic predilection (see "Pharmacology," estrogen receptors). When considering the Framingham study results, the anticipated benefit is 26% to 39% reduction in risk of coronary events in the subset of women with IVSI-401 c/c polymorphism.¹⁰ There are

increased carotid intima-media thickness based on B mode ultrasound were randomly assigned to receive placebo or 1 of 2 HRT regimens (1 mg/day of 17 beta-estradiol continuously along with 0.025 mg of gestodene given from day 17 to day 28 once a month or every third month).^{28,29} After 48 weeks, there was no difference between the placebo and active treatment groups in progression of atherosclerosis measured as a change in carotid²⁸ or femoral²⁹ intima-media thickness.

The HERS findings for ischemic stroke among high-risk women³¹ are consistent with the results of the Women's Estrogen for Stroke Trial.³² In this trial, 664 postmenopausal women who had recently had an ischemic stroke or transient ischemic attack were randomized to receive placebo or ERT as 1 mg/day of 17 beta estradiol. After 2.8 years of follow-up, the relative risk of

also prothrombotic mutations. The risk of MI increased 11-fold in women with a prothrombin mutation 20210GA who took HRT and had hypertension.³⁴

As a result of the WHI findings, new language has been inserted into the CEE,¹¹ combination CEE with MPA (CEE/MPA),³⁵ and conjugated estrogens A, synthetic,³⁶ prescribing information. The new language essentially states that the WHI study reported increased risks of MI, stroke, invasive breast cancer, pulmonary edema, and DVT in postmenopausal women during 5 years of treatment with CEE 0.625 mg combined with MPA 2.5 mg relative to placebo.

Other doses of conjugated estrogens and MPA and other combinations of estrogens and progestins were not studied in the WHI and, in the absence of comparable data, these risks should be assumed to be similar. Therefore estrogens with or without progestins should be prescribed at the lowest effective doses and for the shortest duration.^{11,35,36} In other words, these are class effects and not product specific. (Note: this point differs from the actual monograph presentation to the P&T committee in February 2003 and is updated for this article.)

The FDA announced on January 8, 2003, that all labels on estrogen and estrogen-progestin replacement therapy will be revised to carry a boxed warning that identifies the increased risks of heart disease, heart attacks, strokes, and breast cancer and that these products are not approved for heart disease prevention. Estrogen is still recommended for hot flushes and night sweats but should be used at the lowest doses and for the shortest possible time. For vaginal and vulvar atrophy, vaginal estrogen products are suggested. New labels will state that before using estrogen to prevent osteoporosis, alternative nonestrogen therapies should be considered.³⁷ In the June 2003 prescribing information for the CEE/MPA combination product, the labeling states, "When prescribing solely for the treatment of symptoms of vulvar and vaginal atrophy, topical vaginal products should be considered. . . . When prescribing solely for the prevention of postmenopausal osteoporosis, therapy should only be considered for women at significant risk of osteoporosis and nonestrogen medications should be carefully considered."³⁵ (Note: this point differs from the actual monograph presentation to the P&T committee in February 2003 and is updated for this article.)

Adverse Events

Serum Lipids

Clinical trials have shown that HRT has favorable effects on serum lipids, increasing HDL cholesterol and decreasing low-density lipoprotein (LDL) cholesterol. In one comparative trial of the effects on lipids of oral versus transdermal HRT, the authors reported that transdermal estrogen appears to cause smaller beneficial changes in lipoprotein profiles (about 50% of those brought about by oral administration), possibly because the liver is not exposed to the high estrogen levels obtained

TABLE 6 WHI Results: Summary of CVD Outcomes³³

Outcome	HRT n (%)	Placebo n (%)	Hazard Ratio	Nominal 95% CI
CHD	164 (0.37)	122 (0.30)	1.29	1.02-1.63
CABG/PTCA	183 (0.42)	171 (0.41)	1.04	0.84-1.28
Stroke	127 (0.20)	85 (0.21)	1.41	1.07-1.85
VTE	151 (0.34)	67 (0.16)	2.11	1.58-2.82
Total CVD	394 (1.57)	546 (1.32)	1.22	1.09-1.36

TABLE 7 WHI Results: CHD by Year³³

Year	HRT n (%)	Placebo n (%)	Hazard Ratio*
1	43 (0.51)	23 (0.29)	1.78
2	36 (0.43)	30 (0.38)	1.15
3	20 (0.24)	18 (0.23)	1.06
4	25 (0.32)	24 (0.32)	0.99
5	23 (0.39)	9 (0.16)	2.38
6+	17 (0.33)	18 (0.42)	0.78

*z score for trend across all years = -1.19; test for trend based on Cox proportional hazard model with time-dependent treatment effects.

TABLE 8 HERS CHD Events by Year¹⁸

Year in Trial	Treated Cases	Placebo Cases	Hazard Ratio (95% CI)
1	57	38	1.52 (1.01-2.29)
2	47	48	1.00 (0.67-1.49)
3	35	41	0.87 (0.55-1.37)
4	33	49	0.67 (0.43-1.04)

right after dosing.³⁸

Progestins, both the C-19 nortestosterone derivatives and the C-21 derivatives, cause a dose-related decrease in HDL cholesterol and an increase in LDL cholesterol. The combination of medroxyprogesterone with estrogens tends to attenuate the positive effects that estrogens have on serum lipids. The recent Women's Health, Osteoporosis, Progestin, Estrogen (HOPE) study,³⁹ which looked at data from cycle 6 (6 months of treatment) and cycle 13 (13 months of treatment), showed that the addition of MPA to CEE still elevated HDL, but to a lesser extent than CEE alone. The addition of MPA to CEE also resulted in a slightly smaller decrease in LDL compared with CEE alone, but still significantly greater than placebo. What is troubling is that both CEE alone and a combination of CEE/MPA resulted in an elevation of triglycerides, with the greater increase seen in the CEE-alone group.

Venous Thromboembolism/Thromboembolism

Unlike oral estrogens, transdermal estrogen delivery has no significant effect on production of certain hepatic proteins, renin

TABLE 9 WHI Results: Invasive Breast Cancer Summary by Year³³

Year	HRT No. of Patients (%)	Placebo No. of Patients (%)	Hazard Ratio*
1	11 (0.13)	17 (0.21)	0.62
2	26 (0.31)	30 (0.38)	0.83
3	28 (0.34)	23 (0.29)	1.16
4	40 (0.50)	22 (0.29)	1.73
5	34 (0.57)	12 (0.22)	2.64
6+	27 (0.53)	20 (0.47)	1.12

*z score for trend across all years = 2.56; test for trend based on Cox proportional hazard model with time-dependent treatment effects.

TABLE 10 ERT, HRT, and Breast Cancer

Study	RR (95% CI) ERT Alone	RR (95% CI) Estrogen With Sequential Progestin	RR (95% CI) Continuous Combined
Schairer C. JAMA. 2000. ⁴⁴	1.1 (1.0-1.3)	1.5 (1.0-2.4)	too few cases
Ross RK. JNCI. 2000. ⁴⁵	1.06 (0.97-1.15)	1.38 (1.18-1.68)	1.38 (0.88-1.35)

substrate, sex-hormone-binding globulin, thyroxine-binding globulin, and cortisol-binding globulin. Elevations in these proteins may be associated with some of the adverse effects of oral estrogen therapy, including hypertension, gallbladder disease, and thrombosis, although the clinical significance is not known.^{40,41}

Estrogens and progestins produce a complex variety of effects on coagulation. A history of thromboembolism is a relative contraindication to estrogen therapy.⁴² Progestins may increase or reduce prostacyclin production, but synthetic estrogens increase prostacyclin production. Platelet aggregation is generally unchanged by estrogens, although there is some data to the contrary. Virtually all clotting factors, particularly factors II, VII, IX, X, XII, and fibrinogen, are elevated by synthetic estrogens. The effects on clotting factors are primarily related to estrogen potency. Elevations are relatively marked with ethinyl estradiol but are either not observed or are not clinically significant after use of estrogen patches and ointment or natural estrogens.⁴³

Hypertension

The concern that hypertension may be caused or exacerbated by estrogens has contributed to the belief that hypertension is a contraindication to estrogen therapy. Most clinical evidence shows no causal relationship between ERT and hypertension. Oral estrogen therapy, particularly potent synthetic products, but not transdermal estrogen, causes increased renin substrate and may increase angiotensin II and aldosterone, although the

clinical significance is unknown.⁴³ Progestins produce a dose-related elevation in blood pressure by causing sodium and water retention.¹²

Premenstrual Syndrome

Progestins, when used alone or during the progestin phase of a combination regimen, cause an iatrogenic premenstrual tension-like syndrome. Breast tenderness or mastalgia, bloating, edema, and abdominal cramping, as well as anxiety, irritability, and depression, are frequent complaints. Weight gain, headache, and drowsiness can occur. Approximately 5% of patients are intolerant to all types of progestins, but others may benefit from a dosage reduction or change to another type of progestin.

The 17-hydroxyprogesterone derivatives are used primarily in HRT and are less androgenic but are associated with depression and anxiety symptoms.^{17,41}

Monthly Bleeding

Progestins alone, or given with estrogen in a biphasic manner in a monthly cycle, bring on monthly bleeding in 80% to 90% of women. In contrast, unopposed estrogen causes monthly withdrawal bleeding in 25% of patients. Continuous therapy with a monophasic estrogen-progestin combination is an option for women who wish to avoid monthly bleeding.²⁷

Endometrial Cancer

The increased frequency of uterine cancer from estrogens is related to endometrial hyperplasia, caused by unopposed estrogen therapy.⁴³ Overall, estrogen users have a 4-fold to 8-fold increase (range: 1.7-fold to 20-fold) in risk of developing endometrial cancer relative to the risk in the normal female population of 1 case per 1,000. The addition of progestin to estrogen therapy confers protection against hyperplasia and is generally recommended, either cyclically for at least 10 days per month or continuously in patients with an intact uterus.^{43,46}

Breast Cancer

At year 5, in the WHI trial, notice that the number in the placebo group is 12, which is lower than expected and contributed to the increase in the hazard ratio (Table 9). These data are not stratified by age, which may have been the driver of the breast cancer incidence. If increasing length of time on HRT increased the risk, why does the hazard ratio decline for those who had HRT for 6+ years? There is the thought that the group that had 6+ years of HRT was not powered to see differences. Also at 5 years, there were 2,000 fewer people in the study. There is the possibility that there were preexisting lesions that did not show up until year 4.

One might conclude that the increased risk for breast cancer is from the progestin component. Recall that the patients who received ERT in WHI have not been withdrawn from the study

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TABLE 11 Drug Interactions of Estrogens⁶

Precipitant Drug	Object Drug		Description
Estrogens	Anticoagulants, oral	↓	Estrogens may theoretically reduce the hypoprothrombinemic effect of anticoagulants.
Estrogens	Tricyclic antidepressants	↔	Pharmacologic effects of these agents may be altered by estrogens; the effects of this interaction may depend on the dose of the estrogen. An increased incidence of toxic reactions may also occur.
P450 inducers – barbiturates, rifampin	Estrogens	↓	Coadministration of barbiturates, rifampin, and other agents that induce hepatic microsomal enzymes may produce lower estrogen levels than expected.
Estrogens	Corticosteroids	↑	An increase in the pharmacologic and toxicologic effects of corticosteroids may occur via inactivation of hepatic P450 enzyme.
Hydantoins	Estrogens	↓	Breakthrough bleeding, spotting, and pregnancy have resulted when these medications were used concurrently. A loss of seizure control has also been suggested and may be due to fluid retention.
Estrogens	Hydantoins		

TABLE 12 Drug Interactions of Progestins⁶

Precipitant Drug	Object Drug		Description
Aminoglutethimide	Medroxyprogesterone	↓	Aminoglutethimide may increase the hepatic metabolism of medroxyprogesterone, possibly decreasing its therapeutic effects.
Rifampin	Norethindrone	↓	Rifampin may reduce the plasma levels of norethindrone via hepatic microsomal enzyme induction, possibly decreasing its pharmacologic effects.

because they have not shown an increased risk of breast cancer. Two recently published trials concluded that ERT alone did not increase breast cancer risk (Table 10).

HRT is probably not a carcinogen per se, and does not initiate the turning of a normal cell into a cancer cell, but it might promote cell proliferation of the cancer cell.³⁹

Drug Interactions

See Table 11 for drug interactions of estrogens and Table 12 for drug interactions of progestins.

Dosing and Administration (for Menopausal Symptoms and Osteoporosis Prevention)

Conjugated Estrogens Oral

For the management of moderate to severe vasomotor symptoms associated with menopause, the usual dose is 0.625 mg daily. For atrophic vagina and vulva associated with menopause, the dose is 0.3 mg to 1.25 mg or more daily. It may be administered continuously or cyclically (25 days on drug, 5 days off). If conjugated estrogens are used in the treatment of vasomotor symptoms and the woman is menstruating, administration of the

drug is started on the fifth day of the menstrual cycle. If the woman has not menstruated for 2 or more months prior to the initiation of therapy, administration can be started at any time. For the prevention of osteoporosis, the usual oral dose is 0.625 mg daily, administered in continuous fashion or cyclically (25 days, 5 days off).⁴⁷

Conjugated Estrogens Vaginal Cream

For the management of atrophic vaginitis or kraurosis vulvae, 0.5 g to 2 g of conjugated estrogens can be administered once daily in a cyclical fashion.⁴⁷

Conjugated Estrogens A, Synthetic Oral

For the management of vasomotor symptoms associated with menopause, the initial dose is 0.625 mg daily, with titration up to 1.25 mg daily. For the management of vulvar and vaginal atrophy, the usual oral dose is 0.3 mg daily.^{6,47}

Esterified Estrogens Oral

For the management of vasomotor symptoms associated with menopause, the usual dose is 0.3 mg to 1.25 mg daily in a cyclic regimen. Dosage may be increased to 2.5 mg or 3.75 mg daily if neces-

sary. For kraurosis vulvae, the usual dosage is 0.3 mg to 3.75 mg daily in a cyclic regimen. The cyclic regimen refers to 21 days of drug therapy, followed by 7 days off the drug, and then the cycle is repeated: 1.25 mg daily administered 3 weeks on and 1 week off. If the woman has not menstruated for 2 months prior to initiation of therapy, administration can begin at any time. If the woman has been menstruating, start therapy on the fifth day of the menstrual cycle.⁴⁷

Estradiol Oral

For vasomotor menopausal symptoms and vulval/vaginal atrophy associated with menopause, the dose is 1 mg to 2 mg/day initially in a cyclic regimen. Adjust to control symptoms. Attempt to taper or discontinue medication at 3- to 6-month intervals.⁶ For the prevention of osteoporosis, the usual oral dose is 0.5 mg daily in a cyclic regimen. The drug usually is administered once daily for 21 consecutive days, followed by 7 days without the drug, and then the regimen is repeated.⁴⁷

Estradiol Transdermal

Transdermal estradiol is available in formulations that are applied to the skin once or twice weekly, depending on the individual product. For women with an intact uterus, the transdermal system can be applied cyclically, e.g., 3 weeks on drug followed by 1 week without drug, and then the regimen is repeated. In women who do not have a uterus, the patches should be applied in a continuous fashion.⁴⁷ When used to manage severe vasomotor symptoms associated with menopause or for the management of atrophic vaginitis or kraurosis vulvae or the prevention of osteoporosis, apply patches that deliver an initial dose of 0.025 mg to 0.05 mg/24 hours. For the management of menopausal symptoms, increase dose as necessary and attempt to taper to discontinue every 3 to 6 months.⁶

Estradiol Vaginal Tablet

For the management of atrophic vaginitis, the initial dose is one 25 mcg tablet, intravaginally, once daily for 2 weeks. The maintenance dose is 25 mcg tablet, intravaginally, twice weekly.⁶

Estradiol Vaginal Cream

For the short-term management of atrophic vaginitis or kraurosis vulvae, administer 2 g to 4 g daily for 1 to 2 weeks. Gradually reduce to one half initial dosage for a similar period. A maintenance dose of 1 g given 1 to 3 times a week in a cyclic regimen may be used after restoration of the vaginal mucosa has been achieved.⁴⁷

Estradiol Vaginal Ring

For the management of postmenopausal urogenital symptoms, 1 ring (delivering estradiol 0.0075 mg/24 hours) is inserted into the upper one third of the vaginal vault and remains in place for 3 months. After 3 months, it should be removed and, if needed, replaced.⁴⁷

Estradiol Valerate Injectable

For the management of moderate to severe vasomotor symptoms, atrophic vaginitis, or kraurosis vulvae associated with menopause, the usual dose is 10 mg to 20 mg every 4 weeks.^{6,47}

Estradiol Cypionate Injection

Vasomotor symptoms: intramuscular (IM) injection of 1 mg to 5 mg weekly for 3 to 4 weeks.⁴⁷

Estrone Injectable

For the management of moderate to severe vasomotor symptoms associated with menopause or for the management of atrophic vaginitis or kraurosis vulvae, the usual dose is 0.1 mg to 0.5 mg 2 or 3 times weekly.⁴⁷

Estropipate Oral

For the management of moderate to severe vasomotor symptoms associated with menopause or the management of atrophic vaginitis or kraurosis vulvae, the usual dose is 0.75 mg to 6 mg daily in a cyclic regimen (21 consecutive days on the drug, 7 days off). For the prevention of osteoporosis, the usual dose is 0.625 mg daily in a cyclic regimen (25 days on, 6 days off).⁴⁷

Estropipate Vaginal Cream

For the management of atrophic vaginitis or kraurosis vulvae, the usual dose is 2 g to 4 g of 0.15% estropipate vaginal cream intravaginally once daily.⁴⁷ Administer cyclically, 3 weeks on, 1 week off. For short-term use only.⁶

Ethinyl Estradiol Oral

For the management of vasomotor symptoms associated with menopause, the usual dose range is 0.02 mg to 0.05 mg/day. The dose may be as low as 0.02 mg once every other day. Administer cyclically, 21 days on and 7 days off.^{6,47}

Estrogens and Progestins, Combined

Oral

For the management of moderate to severe vasomotor symptoms associated with the menopause, the management of atrophic vaginitis, or the prevention of osteoporosis, a dose of 0.625 mg conjugated estrogens is given in conjunction with 2.5 mg to 5 mg of MPA once daily in a continuous daily regimen. When a dose of conjugated estrogens is administered in a continuous daily regimen and MPA is administered cyclically, conjugated estrogens are given as a daily dose of 0.625 continuously, while MPA are given as a daily dose of 5 mg on days 15 to 28 of the cycle.⁴⁷

When ethinyl estradiol is used in combination with norethindrone acetate for HRT in the management of moderate to severe vasomotor symptoms associated with menopause or for the prevention of osteoporosis, the usual dose is 5 mcg of ethinyl estradiol combined with 1 mg of norethindrone acetate daily.⁴⁷

Transdermal

For the management of moderate to severe vasomotor symptoms associated with menopause and vulvar or vaginal atrophy, the transdermal patch may be administered as a continuous combined regimen or as a continuous sequential regimen. In the continuous combined regimen, 1 patch delivering 0.05 mg/24 hours of estradiol and 0.14 mg/24 hours of norethindrone (Combipatch) is applied twice weekly. The dosage of norethindrone acetate may be increased by using the dosage system that delivers 0.25 mg/24 hours of norethindrone. In the continuous sequential regimen, a patch delivering 0.05 mg/24 hours of estradiol (Vivelle) is applied twice weekly for the first 14 days of a 28 day cycle, then 1 patch delivering 0.05 mg/24 hour of estradiol and 0.14 mg/24 hour of norethindrone acetate (Combipatch) is applied twice weekly for the remaining 14 days of the cycle.⁴⁷

Two published studies from the Women's HOPE study showed that lower doses of HRT may be as efficacious as the higher dose in treating vasomotor symptoms⁴⁸ and cause less bleeding.⁴⁹

Progestins

There are no convincing data to support the premise that continuous combined HRT reduces progesterone-induced adverse effects relative to sequential HRT.¹⁷ One common regimen is the addition of oral MPA 5 mg to 10 mg daily during the last 10 to 12 days of the cycle.^{6,47} Other progestins used in cyclic therapy include norethindrone 2.5 mg, norgestrol 150 mcg, or micronized oral progesterone 300 mg.¹⁷ This cyclic regimen results in the return of regular menstrual bleeding, which some women find objectionable. An alternative regimen for women for whom bleeding is unacceptable is the continuous administration of estrogens and lower-dose progestins (2.5 mg to 5 mg daily MPA) with the benefit of avoidance of withdrawal bleeding.^{50,51}

Studies of the addition of a progestin for >7 days of a cycle of estrogen use showed a lowered incidence of endometrial hyperplasia. Studies of endometrium suggest that 10 to 14 days of progestin are needed to provide maximal maturation of endometrium and to eliminate any hyperplastic changes. It has not been clearly established that the addition of progestin will provide protection from endometrial cancer. Additional risks, such as adverse effects on lipids, impairment of glucose tolerance, and possible enhancement of mitotic activity in breast epithelial tissue, may be associated with progestin use.²⁷ The results of the WHI trial suggest that progestins increase the risk of CVD, VTE, and breast cancer. (Note: Some injectable formulations are not FDA-approved for menopausal symptoms or osteoporosis prevention so their dosing regimens were not included above.)

Availability

See Table 13 for drug availability, dosing, and costs.

Summary

The HERS,¹⁸ HERS II,^{19,20} and WHI³³ results have changed the

way many clinicians view HRT in menopausal women. The WHI study results have shown that HRT does not protect against CHD. This lack of protection occurs early in treatment, within the first 1 to 2 years. The WHI results in Table 7 show that the hazard ratios for CHD were highest in year 1, at 1.78, and in year 5, at 2.38. However, the high hazard ratio in year 5 may be falsely elevated due to a relatively lower incidence in the placebo arm for that year only.

The HERS trial, which was a secondary prevention trial in postmenopausal women, reported that, after an average of 4.1 years of follow-up, there was no overall difference in CHD endpoints between women randomized to receive placebo or HRT. HRT was given as a continuous combined regimen of 0.625 mg/d of CEE plus 2.5 mg of MPA. Based on a trend of decreasing risk of CHD events with increasing duration of HRT use, the HERS authors speculated that the HERS results were a consequence of domination of the antiatherogenic effects of HRT by early thrombotic effects. The implication was that a net benefit for CHD would have been observed with longer duration of HRT use. However, in HERS II, a study of women recruited to HERS for an additional 2.7 years of follow-up, the anticipated overall net benefit of HRT use for coronary events did not materialize. The lower rates of coronary disease in long-term users of HRT were not sustained. In HERS II, HRT provided no benefit for prevention of ischemic stroke, confirming an earlier report from the randomized portion of HERS.³¹

In the report of the noncardiovascular endpoints of HERS II²⁰ by Hulley, there was an overall increase in the risk of VTE and biliary tract surgery in HRT users. Also, the risk of fracture was not decreased in HRT users in HERS II. This is inconsistent with randomized trials that have established the effectiveness of ERT and HRT in preventing postmenopausal bone loss.^{52,53} The lack of information about use of bisphosphonates and raloxifene after unblinding makes the HERS II findings on fracture somewhat difficult to interpret. In randomized trials, these drugs have been shown to prevent fracture.^{54,55} If more women initially assigned to placebo initiated use of bisphosphonates or raloxifene after unblinding, any benefit of HRT use for fracture prevention would be obscured.

It is possible that ERT might prevent CHD in women free of coronary disease. There is a possibility that many women enrolled in the WHI trial had asymptomatic atherosclerosis. The Estrogen Prevention of Atherosclerosis Trial⁵⁶ provides only limited evidence. This trial assessed the effect of ERT on carotid intima-media thickness in 222 postmenopausal women without pre-existing cardiovascular disease. The women had LDL cholesterol levels of at least 130 mg/dL. They were randomized to receive placebo or 1 mg/day of 17 beta-estradiol. After 2 years of follow-up, the rate of atherosclerosis progression measured as change in intima-media thickness was less in the ERT-treated group than in the placebo group, but the benefit of ERT was limited to women who did not also take lipid-lowering medication.

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TABLE 13 Drug Availability, Dosing, and Cost^{6,47}

Brand Name	Generic Name	Dosage Forms	Dosing Regimen	Cost/30 days (\$)
Premarin oral (Wyeth)	Conjugated equine estrogens (CEE)	oral: 0.3 mg 0.625 mg 0.9 mg 1.25 mg 2.50 mg	1 tablet once daily orally	22.76 28.85 34.50 39.90 53.70
Premarin injectable (Wyeth)	CEE	injection: 25 mg	1 injection of 25 mg that may be repeated in 6-12 hours for emergency treatment of abnormal uterine bleeding	64.75 for 1 injection
Premarin vaginal (Wyeth)	CEE	oral: 0.625 mg/g x 42.5 g	0.5-2 g daily intravaginally	63.38 - 190.14
Cenestin (Barr)	Conjugated estrogens A, synthetic	oral: 0.3 mg 0.625 mg 0.9 mg 1.25 mg	1 tablet once daily orally	20.49 25.97 31.20 36.00
Prempro (Wyeth)	CEE/medroxyprogesterone acetate (MPA)	oral: 0.625 mg/2.5 mg 0.625 mg/5.0 mg	1 tablet once daily orally	39.00 39.00
Premphase (Wyeth)	CEE/MPA	oral: 0.625 mg/5.0 mg	Days 1-14 CEE Days 15-28 CEE/MPA in 1 tablet; 1 tablet once daily orally	39.00
Menest (Monarch)	Esterified estrogens	oral: 0.3 mg 0.625 mg 1.25 mg 2.5 mg	1 tablet once daily orally	9.94 14.13 19.71 18.36
Estratest (Solvay)	Esterified estrogens/ methyltestosterone	oral: 1.25 mg/2.5 mg	1 tablet once daily orally	54.90
Estratest HS (Solvay)	Esterified estrogens/ methyltestosterone	oral: 0.625 mg/1.25 mg	1 tablet once daily orally	44.40
Estradiol (generics)	Estradiol	oral: 0.5 mg 1 mg	0.5 mg qd for osteoporosis prevention; 1-2 mg/d for menopausal symptoms, orally	7.62 10.27 - 20.55
Activella (Novo Nordisk)	Estradiol/norethindrone	oral: 1 mg/0.5 mg	1 tablet once daily	30.69
Ortho-Prefest (Monarch)	Estradiol/norgestimate	oral: 1 mg/0.9 mg	1 tablet once daily	31.47
Estradiol Cream (generic)	Estradiol	intravaginal: 0.1 mg/g x 42.5 g	2-4 grams once daily intravaginally for 1-2 weeks; maintenance doses 1 g 1-3 times a week for 3 weeks	57.34-172.02
Estring (Pfizer)	Estradiol	dermal: 0.0075 mg/24 hrs	1 ring intravaginally for 3 weeks, out for 1 week	104.26
Vagifem (Novo Nordisk)	Estradiol	intravaginal: 25 mcg	1 tablet daily intravaginally for 2 weeks, then 2 times/week maintenance	49.32 for first month, then 21.92 thereafter
Alora (Watson)	Estradiol	dermal: 0.025 mg/24 hr 0.05 mg/24 hr 0.075 mg/24 hr 0.1 mg/24 hr	2 patches/week	31.92 32.61 33.30 34.00
Climara (Berlex)	Estradiol	dermal: 0.025 mg/24 hr 0.05 mg/24 hr 0.075 mg/24 hr 0.1 mg/24 hr	1 patch/week	33.63 33.63 33.63 33.63
Esclim (Women's First Health)	Estradiol	dermal: 0.025 mg/24hr 0.0375 mg/24 hr 0.05 mg/24 hr 0.075 mg/24 hr 0.1 mg/24 hr	2 patches/week	30.80 31.13 31.13 32.30 32.30

(Continued on next page)

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TABLE 13 Availability, Dosing, and Cost^{6,47} (continued)

Brand Name	Generic Name	Dosage Forms	Dosing Regimen	Cost/30 days (\$)
Estraderm (Novartis)	Estradiol	dermal: .05 mg/24 hr 0.1 mg/24 hr	2 patches/week	32.78 35.14
Vivelle (Novartis)	Estradiol	dermal: 0.025 mg/hr 0.0375 mg/hr 0.05 mg/24 hr 0.075 mg/24 hr 0.1 mg/24 hr	2 patches/week	33.34 33.47 34.12 34.84 35.58
Vivelle-Dot (Novartis)	Estradiol	dermal: 0.025 mg/24hr 0.0375 mg/24 hr 0.05 mg/24 hr 0.075 mg/24 hr 0.1 mg/24 hr	2 patches/week	33.48 33.48 34.12 34.84 35.58
Combipatch (Novartis)	Estradiol/norethindrone	dermal: 0.05 mg/0.14 mg/24 hr 0.05 mg/0.25 mg/24 hr	2 patches/week	37.02 38.14
Estradiol valerate (generics)	Estradiol	injection: 20 mg/ml x 10 ml 40 mg/ml x 10 ml	10 mg-20 mg injection once every 4 weeks	13.95
Estrogen cypionate (generics)	Estradiol	injection: 5 mg/ml in 10 ml	1 mg-5 mg injection once every 3-4 weeks	19.98
Estrone (generics)	Estrone	injection: 2 mg/ml x 10 ml 5 mg/ml x 10 ml	0.1 mg-0.5 mg injection 2 or 3 times weekly	14.95
Ortho-Est (Women's First Healthcare)	Estrone	oral: 0.75 mg 1.5 mg	1 tablet once daily orally	42.86 56.15
Estropipate (generic)	Estrone	oral: 0.75 mg 1.5 mg 3 mg	1 tablet once daily orally	12.94 18.60 30.12
Femhrt (Galen)	Ethinyl estradiol/ norethindrone	oral: 5 mcg/1 mg	1 tablet once daily	29.34
Medroxyprogesterone acetate (generic)	Medroxyprogesterone	oral: 2.5 mg 5.0 mg	1 tablet once daily for 14 continuous days in a 28-30-day cycle	4.17 6.30
Aygestin (Wyeth)	Norethindrone	oral: 5.0 mg	1 tablet once daily for 14 continuous days in a 28-30-day cycle	50.40

Costs are based on the average wholesale price per unit in 2003.³⁷ The cost per 30 days was calculated by multiplying the unit cost by the number of doses per month, based on the dosing regimen. For the sake of a fair comparison, costs of continuous dosing regimens only, not cyclic, were used. Dosing regimens for indications other than the treatment of menopausal symptoms and the prevention of osteoporosis were not included, in an effort to make fair comparisons. This table was added in peer review and was not used in the actual monograph. For the PE-T Committee, the author calculated the cost from the pharmacy claims data for the actual patients treated by the IHN. The pharmacy claims data are proprietary and confidential information and could not be used here.

The HOPE study results in 2001 showed that using lower doses of combination therapy such as CEE 0.3 mg/MPA 1.5 mg was just as effective in treating vasomotor symptoms as 0.625 CEE mg alone. The HERS and HERS II trials concluded that HRT did not protect postmenopausal women with CHD from further cardiovascular events. The WHI trial concluded that HRT increased women's risk for breast cancer, VTE, and CHD by 7 to 8 women per 10,000 treated per year.

Delivery of HRT via the transdermal patch delivers more of the drug into the blood stream than oral administration because

ethinyl estradiol is not metabolized by first-pass metabolism when given via this route. Ethinyl estradiol is a much more potent estrogen than its metabolite, estrone. The vaginally administered estrogens also are not subject to first-pass metabolism and deliver the product locally to help treat vaginal atrophy. The estradiol ring and estradiol vaginal tablet are not absorbed systemically and can be used safely in almost any patient if vaginal atrophy symptoms are present.

Most of the medical literature has focused on the combination of CEEs and MPA as standard HRT. This was the HRT ther-

apy used in the HERS and WHI trials. Whether different estrogens or progestins exert different cardiovascular effects remains to be seen. However, the FDA has asked that the prescribing information for all estrogen and estrogen/progestin combination products carry the warnings now found in the conjugated estrogens/medroxyprogesterone products.

As it stands today, the evidence suggests that HRT increases the risks of breast cancer and CHD events in women who already have CHD. It can be presumed that many women in the WHI trial already had undiagnosed CHD, since they were mostly in their sixties at the time of the study and many had cardiovascular risk factors. The FDA is urging that nonestrogen alternatives be considered in the prevention of osteoporosis. HRT is still used for symptoms of menopause but should be used only for the shortest duration at the lowest effective dose. If menopausal symptoms of vaginal atrophy are being treated, vaginally delivered products, which are not systemically absorbed, should be considered first-line therapy.

P&T Committee Recommendations

It had been established some years ago that there is little difference in efficacy or side-effect profiles of the various HRT products. The latest findings suggest that HRT use is associated with an increased risk of breast cancer and cardiovascular disease. Because of this, use should be restricted to the lowest effective dose and shortest duration possible. The FDA has mandated that all HRT products carry warnings in their labels regarding these risks, and these risks are essentially a therapeutic class effect.

Therefore, the choice of products can be made based on economics. At our IHN, the outpatient pharmacy risk is retained by the 5 major health plans in the region. For our P&T committee, the drug coverage status and product placement in each of the formularies of the health plans is a principal focus. In the interest of continuity of care, it is desirable for patients to be able to receive the same medication as inpatients as they would as outpatients. Most women are started on HRT as outpatients. The final P&T decision was to add all of the generic products and the branded products that were available at the second-tier copay (preferred brand) on most of the outpatient drug formularies of the 5 major health plans that insure the patients served by this IHN.

Conclusion

This is an example of a clinical monograph that was used in real-world clinical decision support at an administrative level with input from clinicians (i.e., P&T committee members). This is not an exhaustive review of HRT. There is a much larger body of literature available that evaluates the efficacy of HRT in osteoporosis prevention, for example. This monograph author assumed that P&T committee members, who were practicing pharmacists and physicians, had sufficient knowledge of the older published trials, and, therefore, only the latest pivotal tri-

als were presented. As a result of this monograph, P&T committee members were informed about the current evidence of the risks of HRT and the need to limit therapy to the shortest duration of time.

DISCLOSURES

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